Decision Memo for Autologous Stem Cell Transplantation (AuSCT) for Multiple Myeloma (CAG-00011N)

Decision Summary

It would be optimal if all three questions proposed by HCFA were responded to with well-designed, controlled clinical trials. However, given the low incidence and terminal nature of the disease, as well as a limited number of treatment options currently available to beneficiaries, we believe that the evidence is sufficient to justify a national decision to cover single AuSCT with certain limitations.

The better-designed trials concentrate solely upon patients with newly diagnosed or responsive multiple myeloma. Within this sub-group of myeloma patients, the evidence demonstrates a statistically greater treatment benefit from HDT/AuSCT compared to standard chemotherapy. HDT/AuSCT in refractory multiple myeloma has the weakest evidence. The 1996 BC/BS TEC assessment conducted its review of newly diagnosed or responsive multiple myeloma separate from its review of refractory multiple myeloma. As stated above, TEC concluded that the available evidence demonstrated that HDT/AuSCT was at least as beneficial as standard chemotherapy, and could possibly be better in improving the health outcomes of newly diagnosed or responsive multiple myeloma patients. However, the technology assessment also concluded that the available data did not adequately demonstrate that HDT/AuSCT could improve the health outcomes of patients with refractory multiple myeloma. In addition, there does not appear to be a justification for such intensive intervention in patients with an extremely low tumor burden (usually Durie-Salmon Stage I). The IFM study, as well as other clinical trials, had limited AuSCT candidacy to those with Durie-Salmon Stage II or III patients. Therefore, HCFA has determined that coverage of AuSCT should be limited to Durie-Salmon stage II or III patients with newly diagnosed or responsive multiple myeloma. This would include those patients with previously untreated disease, those with at least a partial response to prior chemotherapy, and those in responsive relapse (using the same definition of partial response). Partial response is defined as a 50% decrease *either* in measurable paraprotein [serum and/or urine] *or* in bone marrow infiltration, sustained for at least one month

Overall, the body of evidence on AuSCT indicates that organ function (cardiac, pulmonary, hepatic, and renal) *must* be adequate prior to transplantation. In order to tolerate the toxic effects of HDT and the stresses of AuSCT, major organ systems cannot be functionally impaired. For example, effective renal clearance is necessary to allow for the filtration of toxic chemotherapeutic by-products. However, given the inherent variability in evaluating the adequacy of cardiac, pulmonary, renal, and hepatic functioning, as previously illustrated, HCFA will not limit coverage by setting organ function standards, allowing this necessary physiological evaluation to be conducted according to community medical practice and individual patient tolerance assessment.

Finally, although the April 2000 BC/BS TEC assessment concluded that the benefits of HDT/AuSCT are applicable to the Medicare population, evidence regarding the issue of age remains speculative. In fact, BC/BS's conclusions were only relevant to the young-old (mid-sixties to mid-seventies). Safety and effectiveness of HDT/AuSCT in older age groups was not addressed. In reviewing the medical literature, HCFA discovered that the oldest multiple myeloma patient that received HDT/AuSCT was 76 (the oldest patient found during BC/BS TEC's review was 77). However, it is unclear just how many patients over age 75 were actually studied. The IFM trial, which presented the most convincing evidence regarding the medical effectiveness of HDT/AuSCT, also used age to limit eligibility. Due to the lack of available evidence on those multiple myeloma patients over age 75 and the well-understood hazards of the procedure which seem to be greater with advancing age, HCFA feels compelled to limit coverage of AuSCT to the young-old Medicare population by setting an upper age limit of 77. We believe that such a limitation is reasonable because (1) no multiple myeloma patients over age 77 were analyzed and (2) the median age at diagnosis is 65 years. At the present time, it is not reasonable and necessary to cover AuSCT in those patients above age 77. HCFA will await further data on elderly multiple myeloma patients, such that any future age limits can be better supported by an evidentiary approach.

In conclusion, HCFA has decided to issue a national coverage determination for AuSCT in the treatment of multiple myeloma that will reflect these limitations:

Single AuSCT is only covered for Durie-Salmon stage II or III patients that fit the following requirements:

1. Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease *either* in measurable paraprotein [serum and/or urine] *or* in bone marrow infiltration, sustained for at least one month), and those in responsive relapse;
2. Adequate cardiac, renal, pulmonary, and hepatic function; and
3. Age $\leq$ 77 years.

Due to insufficient evidence, at this time, tandem transplantation for multiple myeloma remains non-covered. As new evidence requires, we will reconsider this decision. At present, all other uses of AuSCT for multiple myeloma are not covered.

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Decision Memo

To: File: Autologous Stem Cell Transplantation for Multiple Myeloma
CAG-00011

From:

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Re: National Coverage Policy Request
Date: May 31, 2000

This memorandum serves five purposes: (1) describes the etiology of multiple myeloma and treatments currently available; (2) discusses Medicare's coverage history with respect to autologous stem cell transplantation (AuSCT) and outlines current coverage policy; (3) reviews two technology assessments by the Blue Cross/Blue Shield (BC/BS) Technology Evaluation Center (TEC); (4) analyzes relevant clinical literature; and (5) delineates reasons supporting a limited positive national decision to cover single AuSCT for multiple myeloma.

Description and Background of Multiple Myeloma

Multiple myeloma is a malignant disease belonging to a spectrum of hematological disorders known as plasma cell dyscrasias. Malignant plasma cells proliferate and accumulate in a patient's bone marrow, replacing healthy tissue and producing immunoglobulin (Ig) monoclonal proteins. Chromosomal mutations of the Ig genes often found in patients with multiple myeloma indicate that these myeloma cells may originate from antibody-secreting B lymphocytes (B cells). Normal plasma cells (mature B-cells) start out as slowly proliferating plasmablasts found in the lymph nodes. These cells migrate to the bone marrow after stimulation by helper-T cells in the germinal centers. Such stimulation initiates somatic mutations of the Ig genes of B-cells, switching production from IgM to IgG or IgA proteins.

Normal B cells mature (differentiate) quickly, have short life spans, and do not undergo cell mitosis. Perhaps due to genetic abnormalities, malignant myeloma cells, on the other hand, fail to fully differentiate or die, continuing to proliferate in the bone marrow. These malignant cells infiltrate the bone marrow—distorting normal cell configuration—and secrete abnormal amounts of Ig or Ig-fragments. The most common clinical features of multiple myeloma are osteolytic lesions, anemia, renal insufficiency, bone pain, and bacterial infections. Such manifestations often result from tissue damage caused by the development of multiple bone tumors. The vulnerability of patients with multiple myeloma to infection is due to the suppression of normal Ig levels caused by myeloma cells within the bone marrow. The resultant immune dysfunction causes recurrent bacterial infection, the most frequent cause of death for myeloma patients.

Multiple myeloma represents nearly 1% of all cancers and nearly 10% of hematological malignancies. The disorder affects nearly 40,000 people at any one time and accounts for nearly 11,300 deaths annually (1% of all cancer-related deaths). 13,000 Americans are diagnosed with the disease each year.[1] The incidence rate of multiple myeloma for whites in the United States is between one to two cases per 100,000; the rate for African-Americans is nearly twice as high. Incidence of the disease increases with age; the median age at diagnosis is 65 years. Nearly 60% of patients with multiple myeloma are male and less than 30% are younger than 40 years of age.[2] The etiology of multiple myeloma remains poorly understood, however radiation exposure may be a causal factor. A nearly 60% increased risk of multiple myeloma was observed among survivors who entered Hiroshima within three days of the blast. Radiologists, who experience long-term radiation exposure, have a two-fold increased risk of multiple myeloma, despite modern equipment and protective gear.

Available Treatments

Multiple myeloma is a rapidly progressive disease with a median survival (without treatment) of less than one year.[3] Treatment of multiple myeloma has largely been focused around oral chemotherapy regimens. Patients are treated with standard doses of anti-cancer drugs such as melphalan and prednisone (MP). Response rates to standard chemotherapy vary from 40% to 60% with only 5% to 10% of patients reaching a complete remission or response—defined as a disappearance of myeloma proteins from the serum and/or urine *and* a reduction of bone marrow plasma cells to less than 5% for at least three months.[4] Median survival for myeloma patients on standard-dose chemotherapy has been extended to nearly three years;[5] less than 5% survive past ten years. Combination therapies of alternative chemotherapy agents have also been used to treat multiple myeloma patients. Such regimens include the combined use of vincristine, doxorubicin, and dexamethasone (VAD); vincristine, doxorubicin, and methylprednisolone (VAMP); or vincristine, melphalan, cyclophosphamide, and prednisone (VMCP). Research on single versus combination drug regimens indicate that combination therapies do not lead to significantly longer survival rates when compared to MP in most randomized control trials.[6] Interferon alpha therapy has often been used as maintenance therapy and has been shown to prolong the plateau phase (the time between response and relapse) in myeloma patients undergoing chemotherapy.

Given its benefits with other hematologic malignancies, the use of myeloablative, high-dose chemotherapy (HDT) followed by autologous stem cell transplantation (AuSCT) has become the focus of clinical investigation as a possible means of further extending survival for multiple myeloma patients beyond what is attainable with standard chemotherapy regimens. HDT is often used in conjunction with total-body irradiation in which the entire body is subjected to intense unfocused radiotherapy. AuSCT is used to accelerate the restoration of hematopoiesis after aplastic anemia (pancytopenia) that results from the toxicity associated with HDT and/or total body irradiation. In some studies, HDT/AuSCT has induced complete response rates between 20% and 30% and has significantly extended overall survival (OS).[7]

Clinical evidence indicates that younger populations (those less then 65 years) have been able to receive HDT with relatively low treatment mortality (currently less than 5%).[8] An important question that the clinical evidence has not addressed is whether the improvements in outcomes and low treatment-mortality are reproducible within the Medicare population (those either 65 and over, with end-stage renal disease [ESRD], or the disabled). This decision memorandum will examine evidence regarding the effectiveness of HDT and AuSCT compared to standard chemotherapy and its applicability to the Medicare population. It is important to note that, although HDT and AuSCT may be associated with improved outcomes, it is *not* a cure for multiple myeloma. Both standard chemotherapy and HDT/AuSCT are used to extend event-free and overall survival. However, inevitably, nearly all patients with multiple myeloma will relapse.

Description and Current Coverage Policy for Stem Cell Transplantation

Stem cell transplantation is defined as a process in which stem cells, immature cells from which all blood cells develop, are harvested for future intravenous infusion. Blood stem cells can be harvested directly from the bone marrow or from the peripheral blood. These stem cells are treated with drugs to eradicate existing cancer cells and then frozen until transplanted into a recipient.[9] The transplant can be used to effect hematopoietic reconstitution following severely high doses of chemotherapy and/or radiotherapy. There are two main types of bone marrow transplantation: allogeneic and autologous. Allogeneic stem cell transplantation is a procedure in which stem cells or bone marrow is obtained from a healthy donor. AuSCT restores stem cells using the patient's own previously harvested cells.

The *Coverage Issues Manual* addresses Medicare's coverage policy for stem cell transplantation in §35-30.1. National coverage determinations for allogeneic stem cell transplantation have been made for treatment of the following conditions, provided treatment is considered both reasonable and necessary for the individual patient:

- leukemia
- leukemia in remission
- aplastic anemia
- severe combined immunodeficiency disease
- Wiskott-Aldrich syndrome.

Medicare does not cover allogeneic stem cell transplantation for the treatment of multiple myeloma.

National coverage determinations for AuSCT have been made for the treatment of the following conditions, provided treatment is considered both reasonable and necessary for the individual patient:

- acute leukemia in remission with a high probability of relapse and having no human leukocyte antigens (HLA)-matched donor

- resistant non-Hodgkin's lymphomas or presenting with poor prognostic features following an initial response
- recurrent or refractory neuroblastoma,
- advanced Hodgkin's disease upon failing conventional therapy and having no HLA-matched donor

Currently, Medicare does not cover AuSCT for the treatment of the following conditions:

- acute leukemia not in remission
- chronic granulocytic leukemia
- solid tumors (other than neuroblastoma)
- multiple myeloma
- non-primary (AL) amyloidosis (refer to CAG-00050, Decision Memorandum dated 1/14/2000)
- primary (AL) amyloidosis for Medicare beneficiaries over age 64 (refer to CAG-00050)

In the absence of specific coverage policies on other conditions in which stem cell transplantation may be used, Medicare contractors have the authority to develop local medical review policies. In developing local policies, assisted by their Contractor Advisory Committees, contractors must determine that the service is reasonable and necessary. Local medical review policies may vary from one state to another and include instructions limiting the service and/or identifying clinical indications for its use.

The Health Care Financing Administration (HCFA) will limit the analysis in this memorandum to AuSCT for the treatment of multiple myeloma. A coverage determination for allogeneic stem cell transplantation was not requested.

History of Medicare's Coverage Policy Regarding AuSCT for Multiple Myeloma

HCFA has dealt with the issue of AuSCT for multiple myeloma in the past. In September 1992, the HCFA Physicians' Panel convened and discussed the use of AuSCT for the treatment of multiple myeloma. Members acknowledged there were National Institutes of Health (NIH) funded clinical trials then underway looking at the safety and efficacy of the procedure. The Panel recommended that any decision on the issue should be deferred until these trials were completed and their results were reported. HCFA's Technology Advisory Committee (TAC) took up AuSCT again in October 1993 and March 1994. During both meetings, the TAC recommended that HCFA refer this issue to the Office of Health Technology Assessment (OHTA). Blue Cross/Blue Shield Association (BC/BS) Technology Evaluation Center (TEC) came out with its own technology assessment on this procedure in November 1994. The report was unable to draw conclusions on the comparative efficacy of AuSCT in multiple myeloma to standard treatment because of the lack of a randomized clinical trial, small sample sizes, inadequate follow-up, and lack of information on survival and other important endpoints. The OHTA responded back to HCFA in May 1995 citing similar conclusions as those found in the BC/BS report. It was based on this review that HCFA issued a national non-coverage policy on AuSCT for multiple myeloma in May 1996. The *Coverage Issues Manual* states that "effective May 24, 1996, AuSCT for multiple myeloma is a non-covered condition due to insufficient data to establish efficacy."

In October 1996, BC/BS TEC issued another technology assessment on AuSCT for multiple myeloma that drew upon the most recent clinical trial data. BC/BS concluded that the procedure may have potential benefits and recommended the treatment for newly diagnosed or responsive myeloma patients (but not for refractory multiple myeloma). Due to the need for additional medical information, the assessment specifically limited its support for coverage within the confines of national clinical trials. Four months later in February 1997, the TAC revisited the issue and acknowledged the continued evolution of AuSCT for multiple myeloma. However, the committee expressed concerns about the validity and reliability of the clinical studies and the ability to generalize the study's results to the Medicare population. The TAC agreed to uphold HCFA's current non-coverage policy until new scientific information became available.

In August 1999, HCFA internally generated a formal request for the coverage of AuSCT in the treatment of multiple myeloma. Due to the complexity of the available evidence, this issue was sent to the Medicare Coverage Advisory Committee (MCAC). The MCAC had been created to provide independent, expert scientific advice to HCFA in order to assist the agency in making sound, evidence-based coverage NCDs. The MCAC is composed of an Executive Committee (EC) and six individual clinical panels. The EC exists to help provide continuity among the clinical panels and to review, ratify and transmit panel recommendations to HCFA. The Drugs, Biologics, and Therapeutics (DBT) MCAC panel met on September 15 and 16, 1999 to discuss the issue of AuSCT for treatment of multiple myeloma (Attachment C). At the conclusion of the meeting, the panel deliberated and made recommendations based on the questions posed by HCFA.

The EC met on December 8, 1999, and reviewed the DBT panel's recommendations regarding AuSCT for multiple myeloma and did not ratify them (Attachment D). Instead, the EC requested the issue be sent back to the DBT panel for reexamination. As part of their discussions, the EC identified a number of areas where the process could be improved, including the organization and presentation of the clinical evidence. The EC was not commenting on the AuSCT evidence itself or the validity of the recommendations made by the DBT panel, but rather the process in which such recommendations had been crafted. In light of this, the EC agreed to create a model format that could be used by all the clinical panels in reviewing medical evidence and evaluating effectiveness. In the interim, as the EC worked on its recommendations for evaluating medical effectiveness, on January 15, 2000, HCFA requested BC/BS TEC to conduct its own updated, structured review of the medical literature in the form of a technology assessment on HDT and AuSCT in the Medicare multiple myeloma population. HCFA received TEC's report on April 5, 2000. Based on the added strength of the TEC report and the medical literature previously reviewed, HCFA determined it was not necessary to return the issue of AuSCT in multiple myeloma back to the DBT panel, as recommended by the EC.

Blue Cross/Blue Shield Technology Assessments

BC/BS TEC 1996

As mentioned above, in October 1996, BC/BS TEC conducted a technology assessment on HDT/AuSCT in multiple myeloma patients according to the following two indications:

1. Patients with newly diagnosed or responsive multiple myeloma. This included those patients with previously untreated disease, those in either complete response or partial response or remission, and those in responsive relapse.
2. Patients with refractory multiple myeloma. This includes those patients with primary resistant disease and those in resistant relapse.

In examining the first indication, BC/BS TEC conducted a review on data from five controlled studies, including one randomized clinical trial (Attal, *et al*. [1996]), which compared outcomes of HDT/AuSCT to that of standard chemotherapy. In addition, data from fourteen uncontrolled studies were also examined to serve as indirect comparisons of the two treatment modalities. Based upon this review, BC/BS TEC concluded that the available evidence demonstrated that HDT/AuSCT was at least as beneficial as standard chemotherapy, and could possibly be better in improving the health outcomes of newly diagnosed or responsive patients. However, no conclusions were drawn from the evidence as to appropriate patient populations and the prognostic effect of age on health outcomes. Most of the key studies, such as Attal, *et al*. (1996), did not, in fact, include patient groups representative of the Medicare population. The technology assessment indicated that the best strategies for treatment with HDT/AuSCT had not been identified. For example, the report made no definitive conclusions regarding the use of multiple rounds of HDT/AuSCT (tandem transplantation). In its report, TEC recommended that "such patients may derive the greatest benefit from treatment within the context of a randomized trial comparing two or more alternatives methods, at centers with extensive experience in treating myeloma patients with HDT/AuSCT." Given the significant toxicity and morbidity associated with HDT/AuSCT, such treatment seems to only benefit carefully selected patients under strict treatment protocols.

Analysis regarding the second indication (refractory multiple myeloma) was concentrated on three nonrandomized studies with matched controls. In addition, seven uncontrolled trials were examined to serve as indirect comparisons of the two treatment modalities. The data from the three controlled studies and seven uncontrolled trials could not be readily compared with each other, given the significant differences in health outcome measurements and sample populations. There was inconsistency regarding treatment-related mortality among the studies. In comparison to standard chemotherapy, HDT/AuSCT appeared to induce partial response in some patients with resistant multiple myeloma. However, these responses were not associated with an increase in survival for those patients with refractory multiple myeloma. Any survival benefit indicated in these studies could have been due to selection bias that reported data on the healthiest patients. The TEC assessment pointed out that the data "supported the position that for patients with refractory myeloma, those more heavily pre-treated derive less net benefit from HDT/AuSCT than do those less heavily pre-treated." In summation, the technology assessment concluded that the available data did not adequately demonstrate that HDT/AuSCT could improve the health outcomes of patients with refractory multiple myeloma.

BC/BS TEC 2000

In April 2000, BC/BS TEC reexamined the issue of HDT/AuSCT, at the request of HCFA, in order to determine if the clinical evidence was applicable to the Medicare population. This perspective was not addressed in the previous technology assessment. BC/BS TEC considered both past evidence and any new evidence derived from comparative trials that were introduced after the publication of the 1996 report. This newest assessment, which is attached to this memorandum (Attachment E), excluded refractory multiple myeloma patients from its analysis (indication #2 in the 1996 report). Although the data derived from tandem transplantation studies were used in examining the effect of age on treatment outcomes, the comparative effectiveness between single HDT/AuSCT and tandem transplantation was outside the scope of this particular technology assessment, and the topic was not addressed.

Assessing the effect of age on treatment outcome can be a difficult task given the physiological changes associated with aging. Older multiple myeloma patients, who often have a number of comorbid diseases, may not be able to withstand the toxicity of HDT. BC/BS TEC noted the importance of the concept of physiological age, in contrast to chronological age. Age, *per se*, may not be an indicator of prognosis after HDT/AuSCT. Rather, the extent of age-related physiological changes, which can vary regardless of chronological age, may determine a patient's ability to withstand treatment. There is currently no way to quantify physiological age. Thus far, this measurement has been determined subjectively with chronological age being an approximate indicator. In order to focus its review and acknowledge the age-related differences in the Medicare population, the TEC assessment subdivided "older" patients into three categories: the young-old (mid-sixties to mid-seventies), the old-old (mid-seventies to mid-eighties), and the oldest-old (late-eighties and above). The BC/BS technology assessment conducted a review of HDT/AuSCT in multiple myeloma patients according to the following two indications:

1. Disease: Patients with newly diagnosed or responsive multiple myeloma. This included those patients with previously untreated disease, those in a complete or partial remission, and those in responsive relapse.
2. Age: This assessment focuses on "older patients" who are defined to be those patients whose age ranges from mid-sixties to the mid-seventies (the young-old). In the evidence examined, the oldest patient treated with HDT/AuSCT was 77 years old.

The review of the evidence was focused around the following three questions:

1.

   Does recent evidence from comparative studies confirm the earlier conclusions that HDT/AuSCT improves health outcomes in younger patients with multiple myeloma?

   In examining the first assessment question, the BC/BS TEC did not find any new randomized trials comparing HDT/AuSCT to standard chemotherapy. Attal, *et al.* (1996), which was reviewed in the previous assessment, remains the only randomized clinical trial comparing the two treatment modalities. The report reviewed updates of the study, one published update at 60 months follow-up and one unpublished update at 70 months follow-up, in order to determine the durability of the health outcomes. An additional three comparative studies were reviewed, two of which compared outcomes of HDT/AuSCT to standard chemotherapy (Lenhoff, *et al.* [2000] and Barlogie, *et al.* [1997]) and one which compared early HDT/AuSCT to standard chemotherapy followed by late HDT/AuSCT (Fermand, *et al*. [1995]). Consistent with the previous finding by TEC, the results from the two studies comparing HDT/AuSCT to standard chemotherapy also indicated that HDT/AuSCT improves event-free and overall survival. In conclusion, TEC found that the additional data examined remained consistent with the findings in its previous report.

2.

In older patients with multiple myeloma, does HDT/AuSCT improve health outcomes compared to standard chemotherapy?

There were no randomized controlled trials comparing the outcomes of HDT/AuSCT and standard chemotherapy in older patients, nor were there any randomized controlled trials in which such data could be abstracted and compared. Only one published non-randomized controlled study was found that allowed for direct comparison of HDT/AuSCT and standard chemotherapy in older patients (Palumbo, *et al*. [1999]). The report also examined results from unpublished analyses comparing outcomes in older multiple myeloma patients to those in younger patients. Two published studies and two unpublished analyses that reported data separately for older multiple myeloma patients treated with HDT/AuSCT served as indirect comparisons. Two studies that reported outcomes for older patients treated with standard chemotherapy were also used as indirect comparisons. Based upon its review of the available evidence, BC/BS concluded that both the direct and indirect comparisons demonstrate that the improvements seen in younger multiple myeloma patients can be extended to an otherwise similar group of multiple myeloma patients in the young-old age range (mid-sixties to mid-seventies).

3. *Do older patients with multiple myeloma obtain a benefit from HDT/AuSCT that is similar to that obtained by younger patients?*

Two published studies and two unpublished analyses provided direct comparisons between the outcomes of HDT/AuSCT in older multiple myeloma patients versus younger patients. For the purposes of this particular analysis, older patients were defined as those above 60 years of age. Most of these studies excluded patients with poor status or severe comorbid conditions. Event-free and overall survival for older patients were found to be slightly inferior compared to younger patients. However, none of the four studies showed statistically significant differences in health outcomes (event-free and/or overall survival, or treatment-related mortality) in older patients compared to younger patients after receiving HDT/AuSCT.

Although the BC/BS TEC assessment extensively surveys the available evidence, there was not an emphasis on grading such evidence with respect to quality. This raises concerns particularly when data, which had not yet been published, is presented. The report's reliance upon indirect measures to answer the age question can also be problematic. Such comparisons are prone to being influenced by selection bias. In addition, it is possible that selection criteria and treatment protocols may be significantly different, thus making the studies incomparable. Comparisons derived from randomized clinical trials, or, at the very least, controlled prospective trials can mitigate such bias.

Finally, the technology assessment concludes the following: "it appears more likely than not that for multiple myeloma patients in the young-old age range (mid-sixties to mid-seventies) without contraindications to treatment, HDT/AuSCT improves outcomes when compared with outcomes of standard chemotherapy." No mention is made, however, as to which contraindications are relevant to treatment safety and effectiveness. Based upon its review of outcomes data from the Autologous Blood and Marrow Transplant Registry (ABMTR), BC/BS TEC was compelled to state "that outcomes of HDT/AuSCT may be worse than the outcomes of standard chemotherapy if stringent patient selection criteria are relaxed." The importance of careful patient selection was emphasized throughout the report; and yet, the technology assessment did not address which patient populations would benefit (or not benefit) from HDT and AuSCT. Overall, however, the BC/BS TEC conducted a comprehensive review of the evidence on the use of HDT/AuSCT. The information presented in both reports supported the effectiveness of HDT/AuSCT and answered a number of HCFA's questions on the relevancy of the evidence in the Medicare population. However, appropriate patient populations still needed to be identified given the importance of careful patient selection. Consequently, HCFA further examined the clinical evidence in order to attempt to identify an appropriate population for transplant eligibility.

HCFA Analysis of Clinical Evidence

In order to supplement the BC/BS TEC assessments, HCFA reviewed medical literature with the following three key questions in mind:

1. Does the evidence demonstrate that HDT/AuSCT is more effective than standard chemotherapy?
2. Are the results generalizable to the Medicare population (i.e. persons 65 and over, ESRD patients, and the disabled)?
3. What is the appropriate patient population?

Please note that these questions do not involve tandem versus single transplantation. A review of the literature on tandem transplantation was not provided in both TEC assessments. HCFA elected not to undertake such a review in its analysis of the evidence. However, the agency would welcome any future comparative, controlled study data which might support a coverage determination on tandem transplantation.

HCFA has collected bibliographic material (Attachment A) from two major sources:

1. Articles/materials received from field investigators
2. Articles retrieved by HCFA staff in an effort to construct this integrated decision memorandum

This bibliography overlaps with those from the BC/BS TEC assessments (whose structured search criteria have been specified elsewhere). In conjunction with the TEC assessments, HCFA is fully confident that a comprehensive body of evidence has been reviewed on the topic of AuSCT in the treatment of multiple myeloma.

Is the evidence adequate to demonstrate that HDT/AuSCT is more effective than standard chemotherapy?

The key study that addresses the comparative effectiveness of HDT/AuSCT to standard chemotherapy is the prospective, randomized clinical trial conducted by the Intergroupe Français du Myélome (IFM) and presented in Attal, *et al*. (1996). In the IFM trial, 204 previously untreated multiple myeloma patients from 32 French centers and one Belgian center were enrolled between October 1990 and May 1993. These patients were less than 65 years of age, had Durie-Salmon stage II or III myeloma, and were not excluded because of the following: prior treatment, more then one type of cancer, abnormal cardiac and/or liver function, chronic respiratory disease, or psychiatric disease. Prior to randomization, four patients were excluded from analysis (two because of age greater than 65 and two because of violation of study protocols). The remaining 200 hundred patients were randomized into one of two treatments groups. The experimental group (n=100) received four to six alternating cycles of VMCP and BVAP (vincristine, carmustine, doxorubicin, and prednisone). Patients that met the treatment criteria (World Health Organization performance status below 3, creatinine levels under 1.7 mg/dl, and bone marrow that contained more than 200 million nucleated cells per kilogram of body weight) underwent high-dose melphalan and total body irradiation followed by AuSCT. The control group (n=100) received standard chemotherapy which consisted of alternating cycles of VMCP and BVAP. All randomized patients were studied in their assigned group on an intent-to-treat basis.

In the HDT/AuSCT group, 74 patients ultimately proceeded to transplantation while 26 patients did not undergo the treatment on account of death (n=5), poor performance (n=6), abnormal renal function (n=5), and insufficient bone marrow collection (n=10). Exclusions were found to be related to age (18% of patients under 60 did not undergo transplantation versus 42% of those over 60 [p=0.01]). As demonstrated by the following table, HDT/AuSCT had better response rates compared to standard chemotherapy.

Type of Response	Standard Chemotherapy (n=100)*	HDT/AuSCT (n=100)*	Received HDT/AuSCT (n=74)
CR	5	22	22
Very good partial response	9	16	16
Partial response	43	43	32
Minimal	18	7	(not specified)

Type of Response	Standard Chemotherapy (n=100)*	HDT/AuSCT (n=100)*	Received HDT/AuSCT (n=74)
Progressive disease	25	12	(not specified)

*p < 0.001 for standard chemotherapy (n=100) vs. HDT/AuSCT (n=100)

After a median of 70 months follow-up, the median event free survival (EFS) and overall survival (OS) for the standard chemotherapy group were 18 months and 28 months, respectively. The median EFS and OS for the HDT/AuSCT group were 42 months and 57 months, respectively. The following table summarizes the reported probabilities of event-free and overall patient survival at five, six, and seven years. The table contains data from subsequent follow-ups beyond what was reported in the original article, including unpublished data supplied to HCFA.

Outcome	Standard Chemotherapy	HDT/AuSCT	p-value
Probability of EFS after diagnosis	5-year = 10%	5-year = 28%	= 0.01
	6-year = 15%	6-year = 24%	< 0.01
	7-year = N/A	7-year = N/A	
Probability of OS after diagnosis	5-year = 12%	5-year = 52%	= 0.03
	6-year = 21%	6-year = 43%	< 0.03
	7-year = 15%	7-year = 40%	< 0.05

The differences in outcomes between the HDT/AuSCT group and the standard chemotherapy group remain statistically significant after a median of 70 months follow-up. Nearly 40% of patients in the HDT/AuSCT group are projected to be alive in seven years compared to 15% in the standard chemotherapy group.

The IFM trial is the strongest argument in favor of the greater effectiveness of HDT/AuSCT compared to standard chemotherapy. Based upon the relatively stronger design of the IFM trial, other non-randomized studies may be set aside as corroboratory evidence. However, three additional studies (Barlogie, *et al*. [1997], Lenhoff, *et al*. [2000], Alexanian, *et al*. [1994]) that directly compare HDT/AuSCT to standard chemotherapy in newly diagnosed or responsive multiple myeloma patients, are summarized in Attachment B.

The IFM trial is the only trial that randomizes patients between the two treatment modalities. However, there are several issues that need to be addressed. No patients over 65 years of age were included in the trial. Given the toxicity of HDT and the physiological changes that occur with increasing age, the study results may not be transferable to the Medicare population. Furthermore, although randomization can mitigate the potential for selection bias, only 74 patients proceeded to transplantation after induction therapy. Therefore, within the randomized HDT/AuSCT group, patients were still selected out to proceed to transplantation upon meeting additional eligibility criteria. Those patients who might presumably be harmed by the toxic treatment did not continue with the treatment protocol. Had these patients been given the toxic treatment, the ultimate health outcomes for HDT/AuSCT may not have been as statistically favorable. Those patients who did not proceed to transplantation might have lived *longer* than they would have, if they had received HDT. These patients, who survived longer because they did not receive treatment, were then included in the analysis on an intent-to-treat basis. Thus, the results found in the IFM trial may somewhat overstate the effectiveness of AuSCT relative to standard chemotherapy.

Despite the above concerns, neither the IFM nor any other investigative group can be expected to include in their trials a treatment they believe is contraindicated. We should not, and do not, require or expect clinical trial data derived from impossible or ethically questionable comparisons to support Medicare coverage NCDs. However, this issue does speak to the importance of careful patient selection, which was previously alluded to in the discussion of the ABMTR data. It can be reasonably concluded that patients who meet the IFM's initial inclusion criteria (staging, etc.) *and* the transplantation eligibility criteria (creatinine, etc.) will likely benefit more from HDT/AuSCT then standard chemotherapy. HCFA's own review of the clinical evidence, as well as the analyses presented in both BC/BS TEC assessments, suggests that the appropriate boundaries for AuSCT eligibility are those Durie-Salmon Stage II-III patients with newly diagnosed or responsive multiple myeloma.

Are the results generalizable to the Medicare population?

Despite the superior health outcomes of HDT/AuSCT found in these studies, questions regarding the applicability of these results to the Medicare population remain unanswered in several of the larger studies. The IFM clinical trial, as well as the population-based study presented in Lenhoff, *et al*. (2000), excluded patients over 60 years of age. The age cut-off in Alexanian, *et al*. (1994) was set at 62, after treatment-related deaths occurred in four patients between 63 and 69 years of age. In Barlogie, *et al*. (1997), patients up to age 70 were included in the study. However, it was not specified as to how many Medicare-eligible patients were actually enrolled in the study other than a reference that 50% of the sample population was above 50 years old. Given the high toxicity of HDT, unsubstantiated inferences cannot safely be made regarding the relevancy of the above mentioned studies to the Medicare population. HCFA examined two articles that directly compared outcomes of HDT/AuSCT in older patients versus those in younger patients, which are discussed in detail below.

Palumbo, *et al*. (1999) compared outcomes from HDT/AuSCT to outcomes from standard chemotherapy in previously untreated elderly multiple myeloma patients. Patients were eligible if they were 55 to 75 years of age and had normal cardiac, renal, pulmonary, and hepatic function. Patients were excluded if they tested positive for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). Between November 1993 and November 1997, 71 elderly multiple myeloma patients were entered into the study at diagnosis. These patients received two to three courses of VAD as induction therapy followed by an infusion of high-dose melphalan and AuSCT. Instead of using the typical, highly toxic dose of 200 mg/m^2 (shown to be effective in younger multiple myeloma patients) on elderly patients, investigators decreased the melphalan dosage to 100 mg/m^2 (MEL100). These patients were compared to a control group of 71 patients selected among 161 untreated symptomatic patients registered between February 1990 and June 1995 who were treated with standard doses of oral MP. The control group met the same eligibility criteria as the experimental group and patients were matched in pairs by age and beta-2-microglobulin (B2M) levels. Patients were analyzed on an intent-to-treat basis. In the MEL100 group, 89% of patients completed the entire treatment regimen. The following table compares the health outcomes of this group versus the MP group:

Outcome	MEL100/AuSCT	MP	p-value
Complete Response	47%	5%	< .01
Probability of EFS from start of treatment	4-year = 33% (median 34 months)	4-year = 14% (median 17.7 months)	< .001
Probability of OS from start of treatment	4-year = 71% (median 56+ months)	4-year = 52% (median 48 months)	< .01

Age was not found to be a significant prognostic indicator of treatment outcome, using both univariate and multivariate analyses.

Siegel, *et al*. (1999) looked at whether age was a biologically adverse factor in previously treated multiple myeloma patients receiving high-dose melphalan with AuSCT. From a population of 900 patients enrolled in tandem transplantation trials, 49 patients ages 65 or older (with a minimum of 18 months follow-up) were identified (age range 65-76 years; median 67). Drawn from a population of 501 younger patients who were also treated with tandem transplantation, 49 pair mates (age range 37-64 years; median 52) were matched to the 65 and older group using a standardized Euclidian distance measure on the following prognostic factors: B2M, albumin, creatinine, C-reactive protein, and the presence or absence of unfavorable chromosomal abnormalities. All patients received the first cycle of HDT/AuSCT. The incidence of complete response was lower in the older group (20% versus 43%, p=0.02). Complete response duration, EFS, and OS were, however, comparable. Age was not identified as an adverse risk factor for either EFS or OS, using a multivariate analysis.

As indicated in Attachment B, serious selection biases exist within both studies. It is unclear how patients were selected and from which patient populations they were drawn. As a result, the viability of both studies, as strong controlled trials, is called into question. Furthermore, Siegel, *et al*. reported that one third of its patients had refractory multiple myeloma, which potentially distorts the value of such age-related inferences when applied to the newly diagnosed/responsive population. Unlike the IFM study, which was able to support the efficacy of AuSCT, there is no straightforward evidence with respect to the effects of age upon treatment outcome. Consequently, the April 2000 BC/BS TEC assessment chose to address the issue of HDT/AuSCT in patients in the young-old age group by enumerating multiple data sets (often unpublished) which provided indirect evidence on treatment effectiveness.

What is the appropriate patient population?

It should be emphasized that both TEC assessments only support the use of AuSCT in patients with either newly diagnosed or responsive multiple myeloma, but HCFA will consider any new evidence on refractory multiple myeloma. In determining whether response to induction therapy is an adequate criterion for transplant eligibility, one is faced with designating a working definition of "responsiveness." As documented in Attachment B, the primary studies have slightly differing set of definitions for both complete and partial response (or remission). However, the critical component for assessing transplant eligibility involves establishing a threshold for partial response, since utilizing complete response would likely constitute an overly stringent evidentiary standard. Gore, *et al*. (1989) provides a feasible, fair definition of partial response: a 50% decrease *either* in measurable paraprotein [serum and/or urine] *or* in bone marrow infiltration, sustained for at least one month.

In addition, one should consider favorable prognostic factors such as B2M and creatinine levels that might help direct AuSCT eligibility. A separate, directed literature review on such prognostic factors has not been included as part of this current evaluation. HCFA will entertain additional evidence that may emerge in this area. Any new putative prognostic factor must successfully pass three steps of testing (Burke, *et al*. [1999]) before it can be used clinically:

1. Discovery, characterization, and predictive accuracy assessment (e.g., area under the receiver operator characteristic curve) of the factor in a defined population. The factor must be sufficiently characterized so that it can be independently replicated.
2. Replication of predictive accuracy results across methods by independent investigators in the defined population in the context of the other relevant prognostic factors.
3. Validation in its intended clinical population. The factor must be powerful enough to overcome intra-observer, inter-observer and inter-institutional variation.

A review of the clinical studies (Attachment B) indicates, for example, that B2M levels might serve as a prognostic factor, even though none of the trials actually used B2M as an eligibility criterion, but only as a matching factor. B2M is a low molecular weight protein derived from the light chain of HLA class 1 molecules and is found on the cytoplasmic membranes of all nucleated cells.[10] In addition to Durie-Salmon staging, circulating B2M can also reflect the degree of tumor burden. Other prognostic factors, such as the labeling index (and interleukin 2, are beyond the scope of both this discussion.

Although the adequacy of the above steps 1 and 2 are outside the scope of the current evaluation, it becomes clear that there are critically important validation issues. In the available studies, the most common approach was to report the significance of a factor in a multivariate model. However, significance is not necessarily synonymous with predictive accuracy.[11] It is also necessary to assess the accuracy of a factor in a multivariate model. Unfortunately, none of theses studies report the predictive accuracy of their factors. Three studies considered the significance of B2M in newly diagnosed/responsive multiple myeloma using a multivariate model:

Study	Multivariate Regression Results For B2M	Cut-Off Used For B2M
Attal, *et al*. (1996)	$p < 0.001$for both EFS and OS	Not specified
Cunningham, *et al*. (1994)	Not significant	4.0 mg/L
Palumbo, *et al*. (1999)	$p = 0.04$ for both EFS and OS	4.0 mg/L

Aside from the obvious discrepancy in significance between Cunningham, *et al*. and the other two studies, there are also other fundamental issues that suggest insufficient validation. First, one must emphasize that these three studies have not been designed for the purpose of assessing B2M as a prognostic factor. Such analyses have been secondary to the primary study question of medical effectiveness. There is a need for epidemiological studies to formulate the proper questions and account for confounding variables. Second, the most appropriate threshold (or cut-off) for B2M levels, as a prognostic indicator of treatment outcome, remains unclear. Finally, the transformation of continuous laboratory results into discrete (binary) values inherently reduces the factor's predictive accuracy.

In lieu of unsubstantiated prognostic factors, HCFA should at least tie coverage to adequate cardiac, pulmonary, hepatic and renal function. Although it is tenuous to use a fixed of set diagnostic parameters for transplant inclusion/exclusion, it is worthwhile to enumerate those five studies reviewed by HCFA that define specific physiologic criteria for these organ functions (these studies are not solely restricted to newly diagnosed or responsive multiple myeloma):

Study	Renal Exclusions	Hepatic Exclusions	Cardiac Exclusions	Pulmonary Exclusions
Attal, *et al*. (1996)	Creatinine > 1.7 mg/dL	N/A	Systolic ejection fraction < 50% or abnormal stress test	Vital capacity or carbon monoxide diffusion capacity < 50%
Barlogie, *et al*. (1997)	Creatinine > 2 mg/dl	N/A	Systolic ejection fraction < 50%	Carbon monoxide diffusion capacity < 50%
Cunningham, *et al*. (1994)	Glomerular filtration rate < 30 ml/min	N/A	Previous ischemic heart disease	Previous chronic bronchitis
Fermand, *et al*. (1998)	Creatinine > 3 mg/dl	N/A	N/A	N/A
Jagannath, *et al*. (1997)	Creatinine > 3 mg/dl	Liver function abnormalities at least 2x upper range of normal	Left ventricular ejection fraction < 50%	Forced vital capacity and carbon monoxide diffusion capacity < 50%

It is not possible to generate a highly structured, optimal pre-transplant performance profile from such a limited data set, particularly since there are a number of studies that did not specifically document organ-based requirements for transplant eligibility. Although it may appear convenient to select certain eligibility markers, such as creatinine levels less than or equal to 3 mg/dL, merely highlighting one such "sentinel" parameter will fail to emphasize the necessary orchestration of physiological function across *all* major organ systems. In a given patient, a transplant team's decision to proceed (or not to proceed) with AuSCT is highly complex, and not dependent upon a fixed battery of diagnostic tests. However, the above table can hopefully serve as a consultative resource, in the absence of tightly-circumscribed, prescriptive evaluation requirements.

National Coverage Determination

It would be optimal if all three questions proposed by HCFA were responded to with well-designed, controlled clinical trials. However, given the low incidence and terminal nature of the disease, as well as a limited number of treatment options currently available to beneficiaries, we believe that the evidence is sufficient to justify a national decision to cover single AuSCT with certain limitations.

The better-designed trials concentrate solely upon patients with newly diagnosed or responsive multiple myeloma. Within this sub-group of myeloma patients, the evidence demonstrates a statistically greater treatment benefit from HDT/AuSCT compared to standard chemotherapy. HDT/AuSCT in refractory multiple myeloma has the weakest evidence. The 1996 BC/BS TEC assessment conducted its review of newly diagnosed or responsive multiple myeloma separate from its review of refractory multiple myeloma. As stated above, TEC concluded that the available evidence demonstrated that HDT/AuSCT was at least as beneficial as standard chemotherapy, and could possibly be better in improving the health outcomes of newly diagnosed or responsive multiple myeloma patients. However, the technology assessment also concluded that the available data did not adequately demonstrate that HDT/AuSCT could improve the health outcomes of patients with refractory multiple myeloma. In addition, there does not appear to be a justification for such intensive intervention in patients with an extremely low tumor burden (usually Durie-Salmon Stage I). The IFM study, as well as other clinical trials, had limited AuSCT candidacy to those with Durie-Salmon Stage II or III patients. Therefore, HCFA has determined that coverage of AuSCT should be limited to Durie-Salmon stage II or III patients with newly diagnosed or responsive multiple myeloma. This would include those patients with previously untreated disease, those with at least a partial response to prior chemotherapy, and those in responsive relapse (using the same definition of partial response). Partial response is defined as a 50% decrease *either* in measurable paraprotein [serum and/or urine] *or* in bone marrow infiltration, sustained for at least one month

Overall, the body of evidence on AuSCT indicates that organ function (cardiac, pulmonary, hepatic, and renal) *must* be adequate prior to transplantation. In order to tolerate the toxic effects of HDT and the stresses of AuSCT, major organ systems cannot be functionally impaired. For example, effective renal clearance is necessary to allow for the filtration of toxic chemotherapeutic by-products. However, given the inherent variability in evaluating the adequacy of cardiac, pulmonary, renal, and hepatic functioning, as previously illustrated, HCFA will not limit coverage by setting organ function standards, allowing this necessary physiological evaluation to be conducted according to community medical practice and individual patient tolerance assessment.

Finally, although the April 2000 BC/BS TEC assessment concluded that the benefits of HDT/AuSCT are applicable to the Medicare population, evidence regarding the issue of age remains speculative. In fact, BC/BS's conclusions were only relevant to the young-old (mid-sixties to mid-seventies). Safety and effectiveness of HDT/AuSCT in older age groups was not addressed. In reviewing the medical literature, HCFA discovered that the oldest multiple myeloma patient that received HDT/AuSCT was 76 (the oldest patient found during BC/BS TEC's review was 77). However, it is unclear just how many patients over age 75 were actually studied. The IFM trial, which presented the most convincing evidence regarding the medical effectiveness of HDT/AuSCT, also used age to limit eligibility. Due to the lack of available evidence on those multiple myeloma patients over age 75 and the well-understood hazards of the procedure which seem to be greater with advancing age, HCFA feels compelled to limit coverage of AuSCT to the young-old Medicare population by setting an upper age limit of 77. We believe that such a limitation is reasonable because (1) no multiple myeloma patients over age 77 were analyzed and (2) the median age at diagnosis is 65 years. At the present time, it is not reasonable and necessary to cover AuSCT in those patients above age 77. HCFA will await further data on elderly multiple myeloma patients, such that any future age limits can be better supported by an evidentiary approach.

In conclusion, HCFA has decided to issue a national coverage determination for AuSCT in the treatment of multiple myeloma that will reflect these limitations:

Single AuSCT is only covered for Durie-Salmon stage II or III patients that fit the following requirements:

1. Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease *either* in measurable paraprotein [serum and/or urine] *or* in bone marrow infiltration, sustained for at least one month), and those in responsive relapse;
2. Adequate cardiac, renal, pulmonary, and hepatic function; and
3. Age $\leq$ 77 years.

Due to insufficient evidence, at this time, tandem transplantation for multiple myeloma remains non-covered. As new evidence requires, we will reconsider this decision. At present, all other uses of AuSCT for multiple myeloma are not covered.

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[1] Siegel, *et al.* (1999).
[2] Blue Cross/Blue Shield (1996).
[3] Blue Cross/Blue Shield (1996).
[4] Gore, *et al.* (1989).
[5] Gahrton (1999).
[6] Gahrton (1999).
[7] Bataille, *et al.* (1997).
[8] Siegel, *et al.* (1999).
[9] National Cancer Institute/PDQ Glossary found at cancer.med.upenn.edupdq_html/glossary/psct.aspl.
[10] Lee, *et al.* (1998).
[11] Burke, *et al.* (1999).

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